## REMARKS/ARGUMENTS

Claims 17-20, 22-30, 67 and 69-72 are pending in this application. Claims 27, 67, 70, 71, and 72 have been amended. Support for the amendments in claims 27 and 67 are at least at page 7, last line; page 7, line 24; page 20, lines 19-29; page 17, line 13; and the sentence bridging pages 7 and 8. The rest of the amendments are of formal nature. All amendments are fully supported by the specification as originally filed, and do not add new matter.

All amendments and cancellations were made without prejudice or disclaimer, and without acquiescence to any of the rejections, or the reasoning underlying the rejections. Applicants specifically reserve the right to pursue any deleted subject matter in one or more continuing applications.

### *Interview Summary Record*

Applicants wish to express their thanks to the Examiner for the opportunity to discuss the outstanding rejections during a telephone interview on May 2, 2006, between the Examiner, the undersigned attorney and inventors Dr. Roland Buelow and Dr. Wim van Schooten. During the interview, the rejections under 35 USC 102 and 103, and, in particular, the differences between the vectors disclosed in U.S. Patent No. 5,569,85 (Lonberg et al.) and the vectors claimed in the present application, as well as the differences between the methods disclosed in U.S. Patent No. 5,202,238 (Fell et al.) and Rader et al. (J. Biol. Chem., Vol. 275, No. 18, 13668-13676) and the methods claimed in the present application were discussed. The current claim amendments serve to more clearly reflect such differences, as discussed during the interview.

### *Claim Rejections - 35 U.S.C. § 102*

(1) Claims 17-20, 22-26, 67, and 69-71 remained rejected under 35 USC 102(b) as allegedly being anticipated by U.S. Patent No. 5,569,825 (1996), hereinafter referred to as "Lonberg et al."

The rejection is respectfully traversed.

According to the rejection, Lonberg et al. teaches transgenic vectors useful for making transgenic rabbits (an animal generating antibody diversity primarily by gene conversion), including human Ig gene segments flankedby non-coding sequences derived from a non-human

animal, such as rabbit. Regarding the functional requirement that the humanized Ig locus included in the vectors of the present invention is "capable of undergoing gene conversion . . . in the non-human animal," the Examiner noted that "by following the teachings of Lonberg to use the transgenic vectors to make transgenic rabbits, the encoded immunoglobulin loci would be in an environment favoring gene conversion over rearrangement." From this, the Examiner concluded that the transgene construct of Lonberg et al. meets the claim requirement as being capable of undergoing gene conversion.

Claim 67 has been amended to more clearly reflect the structural features characterizing the transgenic vectors claimed. In particular, claim 67 now recites that (i) the vectors contain multiple V gene segments, at least one which is a functional V gene segment encoding a human V region amino acid sequence, (ii) at least one of the functional V gene segments encoding a human V region amino acid sequence is placed downstream of the other V gene segments, and (iii) the V gene segments present in the vectors are separated only by non-coding, non-human sequences. These vectors significantly differ from the vectors of Lonberg et al.

The non-coding sequences of animal origin mentioned in column 8, lines 6-36 of the Lonberg et al. patent are isotype switch sequences, which are linked to heavy chain constant region ($C_H$) genes, and serve to support isotype switching of the heterologous transgene in B-cells of the transgenic animal. Since claim 67, as currently amended, clearly recites that in the vectors of the present invention non-coding, non-human sequences separate V region sequences, this disclosure of Lonberg et al. does not anticipate claim 67.

The only additional mention of non-coding sequences of non-human origin is in the first paragraph of column 9 of Lonberg et al. This disclosure concerns short regulatory sequences, such as, for example, the combination of human immunoglobulin gene segments with a rodent immunoglobulin enhancer sequence. Since the vectors of Lonberg et al. are constructed starting with a human Ig locus, they, as a result, comprise an Ig translocus in which the V region sequences are flanked and separated by predominantly human non-coding sequences. Even if a non-human regulatory sequence mentioned in column 9 are present, the non-coding sequences separating the V region gene sequences are overwhelmingly human. In contrast, in the vectors

claimed in claim 67 the V region sequences are separated solely by non-coding, non-human sequences. Accordingly, Lonberg et al do not anticipate claim 67.

Claims 17-20, 22-26, and 69-71 all depend, directly or indirectly, from claim 67, carrying its recitations. Hence, Lonberg et al. do not anticipate these claims either.

In view of the foregoing analysis and the recent claim amendments, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

***Claim Rejections – 35 USC § 103***

The rejection of claims 27-30 under 35 USC 103(a) as allegedly being unpatentable over U.S. Patent No., 5,202,238 (1993) (Fell et al.) in view of Rader et al. (J. Biol. Chem. 275(18):13668-13676 (2000)) was maintained from the Office Action.

In addressing Applicants' earlier arguments, the Examiner notes that "the vector taught by Fell et al. contains the entire murine heavy chain including introns and murine regulatory sequences, wherein only the coding region of a murine variable region gene or constant region gene is replaced by a human variable or constant region gene." Thus, according to the rejection, "the vectors taught by Fell et al. in fact contain non-human regulatory sequences and the introduced human gene is in fact flanked by non-coding non-human sequences." Rader et al. was cited as allegedly providing motivation for making chimeric rabbit antibodies over murine antibodies.

Claim 27 has been amended to clearly recite that the claimed method is directed to the preparation of vectors that contain multiple V gene segments, at least one which is a functional V gene segment encoding a human V region amino acid sequence, at least one of the functional V gene segments encoding a human V region amino acid sequence is placed downstream of the other V gene segments, and the V gene segments present in the vectors are separated only by non-coding, non-human sequences. Such method is neither taught nor suggested by the combination of Fell et al. and Rader et al. The structural differences between the vectors of Fell et al. and those produced by the method of claim 27 of the present application are very significant, since they are needed to provide for efficient antibody diversification in animals that produce antibody diversity primarily by gene conversion. When transgene constructs of different structure, such as the constructs of Fell et al., are transferred into gene converting

animals, antibody diversity will be created predominantly by gene rearrangement. The result of this process, which is rather inefficient in gene converting animals, is a repertoire of low affinity antibodies, each of which will contain a variable region sequence encoded by a single V gene segment. In contrast, as recited in claim 27, the vectors of the present invention allow the production of a functional repertoire of humanized antibodies with V region amino acid sequences encoded by more than one V region gene segment, in gene converting animals.

In view of the foregoing arguments and the current claim amendments, Fell et al. and Rader et al. do not make obvious the invention claimed in claim 27. Since claims 28-30 depend, directly or indirectly, on claim 27 carrying its recitations, they are not obvious over the cited combination of references either. Accordingly, the Examiner is respectfully requested to reconsider the present rejection.

***Claim Rejections – 35 USC § 112***

Applicants note the Examiner's comment concerning the missing underlining of the word "flanked" in the previous amendment. It is believed that the current claim amendments are in full compliance with the requirements of 37 CFR 1.121(c).

***Claim Objections***

Claim 72 was objected to for being dependent upon a rejected base claim, but was indicated as allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Since it is believed that all claims as currently pending are allowable, claim 72 has not been rewritten in an independent form.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing **Attorney's Docket No. 39691-0005 A**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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